



Received on 19 August 2020; received in revised form, 11 February 2021; accepted, 24 May 2021; published 01 October 2021

A SYSTEMATIC REVIEW OF UNANI FORMULATIONS FOR POTENTIAL IN TREATMENT OF HEPATOCELLULAR CARCINOMA

Z. A. Shaikh¹, S. S. Kamyab¹, M. M. Deshpande², G. J. Mulla³, N. S. Bhatt² and A. S. Moghe^{*1}

Department of Cell and Molecular Biology¹, Rajiv Gandhi Institute of IT & Biotechnology, Bharati Vidyapeeth Deemed to be University, Pune - 411045, Maharashtra, India.

Department of DravyagunaVigyan², BVDU College of Ayurveda, Pune - 411043, Maharashtra, India.

Department of Physiology³, Z. V. M. Unani Medical College and Hospital, Pune - 411001, Maharashtra, India.

Keywords:

Chronic liver disease, Hepatocellular carcinoma, Phytochemicals, Unani formulations, Unani medicine

Correspondence to Author:

Dr. Alpana S. Moghe

Associate Professor,
Department of Cell and Molecular
Biology, Rajiv Gandhi Institute of IT
& Biotechnology, Bharati Vidyapeeth
Deemed to be University, Pune -
411045, Maharashtra, India.

E-mail: alpanasm@gmail.com

ABSTRACT: Background: Hepatocellular carcinoma (HCC) represents the third most common cause of death in the world. It is resistant to most chemotherapeutics and associated with a poor prognosis. Unani system of medicine offers effective treatment for various chronic liver diseases. These treatments have shown reversal of inflammation and fibrosis in various clinical conditions. In the present study, we have reviewed Unani formulations to identify plant drugs that are valuable for the development of novel and effective drugs in management of HCC. **Method:** PubMed and Google Scholar were searched using mesh terms 'hepatocellular carcinoma'; 'liver diseases' 'name of individual Unani formulation and plant drug'. The outcome of interest included formulations used for liver diseases; phytochemical and pharmacological information of individual plant drugs. The additional information sources were the National Formulary of Unani Medicine and Unani Pharmacopoeia of India (Formulation). The outcome of interest was the composition and applications of formulations prescribed for liver diseases. **Result:** Total of 710 unique formulations were searched, out of which 59 formulations having hepatoprotective, hepatotonic, deobstruents, and astringent activity was selected for the present study. They were reviewed for individual ingredients. About 16 plant drugs among these were repeated in more than 7 formulations, each having a specific role in treatment options. They were further searched using PubMed and Google Scholar for phytochemical content and pharmacological activity and were found to have a high potential for use in HCC. **Conclusion:** The exhaustive review of 59 Unani formulations used for the treatment of liver dysfunctions identified about 16 traditionally proven plant drugs for exploration in the treatment of HCC.

INTRODUCTION: The liver is a glandular organ of digestive system. It has a complex role in metabolism of the body. More than 100 vital functions are known to have an association with the liver.

Some of its important functions are regulation of metabolic pathways, storage of glycogen, secretion of hormones, synthesis of protein, detoxification, digestion, and decomposition of RBC¹. Progressive destruction and regeneration of liver parenchyma are commonly observed pathological processes that lead to various chronic liver diseases. Viral hepatitis, alcoholic or non-alcoholic fatty liver disease, autoimmune hepatitis, cirrhosis, and hepatocellular carcinoma are a few of the commonly observed chronic liver diseases².

QUICK RESPONSE CODE



DOI:

10.13040/IJPSR.0975-8232.12(10).5253-63

This article can be accessed online on
www.ijpsr.com

DOI link: [http://dx.doi.org/10.13040/IJPSR.0975-8232.12\(10\).5253-63](http://dx.doi.org/10.13040/IJPSR.0975-8232.12(10).5253-63)

Excessive alcohol consumption, virus infection, obesity, diabetes, and drug-induced liver damage are the main causative factors. About 3.9 to 6.9 deaths per 100,000 populations are caused due to chronic liver diseases in various regions of the world³.

Progression of chronic liver diseases to hepatocellular carcinoma is not uncommon in India. Approximately 22,000 new cases of primary liver cancer are reported annually in the country. The incidence of secondary liver cancer is about twenty times higher than primary cancer. HCC is very complex and unique when compared with other cancer types. It is mostly associated with chronic liver diseases such as hepatitis or cirrhosis from any cause. They influence each other as cirrhosis is a precursor for most HCC, and growing HCC deteriorates liver function. Moreover, HCC has resistance to a large array of toxins and most chemotherapeutics. Several clinical trials have attempted to overcome the resistance with high doses of chemotherapeutic agents. Such attempts have, however, failed to produce any meaningful survival advantage for patients with HCC. Another characteristic feature of HCC is the natural tendency of HCC cells to invade the portal vein and grow in its lumen, which can get carried away by the bloodstream resulting in distant metastasis. These adversities of HCC impose significant restrictions on treatment options. Treatment such as surgical resection, ablation, chemoembolization is useful only to selected patients.

Protein kinase inhibitors like sorafenib enhance survival for only a short period. Overall very low (4%) survival rate of HCC underlines the limitations in treatment options and marks it as a cause of major health burden. At present, liver transplantation remains the only curative option for patients with cirrhosis and end-stage liver diseases⁴.

The Unani system of medicine is one of the oldest traditional medicinal systems which has been offering treatments for chronic liver diseases and cirrhosis for centuries. A large number of single and compound drug formulations are documented to have benefits over chronic liver conditions. These formulations are mostly used for antifibrotic and liver regenerative effects⁵.

The pioneer of the Unani system of medicine the great Roman physician Galen 129– 217 (A. D.) described the liver as a counterpart of the sun which is a source of energy for other planets⁶. The Unani system of the medicine referred to the liver as an organ responsible for the production of humor (*Akhlat*) which are named as sanguine (*Dam*), phlegm (*Balgum*), yellow bile (*Safra*) and black bile (*Sauda*). The liver is also identified as an organ that produces four vital powers (*Quwa*), namely the power of absorption (*Quwat-e-jaziba*), power of digestion (*Quwat-e-ghaziya*), power of retention (*Quwat-e-masikah*), and power of excretion (*Quwat-e-dafiya*). It is also known to be an organ responsible for the production of innate heat (*hararat-e-gariziya*)⁷. An appropriate balance of these forces and humor are necessary for maintaining a healthy metabolic state of the liver.

The imbalance in any of these may lead to pathological changes via alteration in the temperament of humor. The options for treatment of chronic liver diseases are based on measures for correction of altered temperaments, evacuation of morbid matter, and empowerment of liver.

The reviews on therapeutic principles of liver diseases in the Unani system of medicine have earlier been published by Shabnam Ansari (2015)⁸ Aisha Siddique (2017)⁹ and Mohammad Siddiqui (2015)¹⁰. Shabnam Ansari *et al.* have summarized various pathological conditions of the liver as *Su-e-Mizaj* [Abnormal / Pathological temperament of the Liver], *Zauf-e Jigar* [Dullness of Liver, hepatosisor Hypocholeretic], *Sudda-e-Jigar* (Hepatic obstruction), *Dard-e-Jigar* (Hepatalgia), *Warm-e-Jigar* (Hepatitis), *Zarba-e-Jigar* (Trauma), *Dabila-e-Jigar* (Hepatic Abscess), *Segar-e-jigar* (Cirrhosis of Liver), *Su-ul-Qinaya* (Anaemia) and *Istiska* (Ascites)". The review has described diagnosis and treatment options offered in the Unani system of medicine and pointed out the drugs which are useful in the treatment of all kinds of liver ailments. They included Kasani (*Cichorium intybus*), karafs (*Apium graveolens*), Ghafis (*Gentiana olivieri*), Izkhar (*Cymbopogon jwarancusa*), Kishneez (*Coriandrum sativum*), Kasoos (*Cuscuta reflexa*), Mundi (*Sphaeranthus indicus*), Turmus (*Lupinus albus*) having properties of astringent, diuresis and deobstruents⁸.

Ayesha Siddiqui *et al.*, have described various temperaments of the liver as an indicator of a normal or pathological state. The normal temperament (*Mizaj*) of liver is hot (*Haar*) and moist (*Ratab*). Due to excessive consumption of alcohol, erratic dietary habits, excess fatty foods its temperament (*Mizaj*) gets altered to cold (*Barid*) and dry (*Yabis*) which is not acceptable to the liver. This leads to pathological changes allowing the accumulation of morbid matter (*Akhlat-e-Galiza*) in the liver⁹. Mohammed Akhtar Siddiqui *et al.*, (2015) presented various case studies demonstrating a significant decrease in fibrosis and improvement in liver functions due to systematic treatment in patients with decompensated liver cirrhosis¹⁰. These findings emphasized the potential of Unani medicines in the treatment of chronic liver diseases.

The therapeutic benefits offered by the well-defined Unani system of medicine have however not been explored for the development of drugs in the management of advanced-stage liver diseases such as HCC. In the present review paper, we have attempted to survey the potential of Unani drugs for search of novel drug leads against HCC. All the formulations prescribed in the National Formulary of Unani Medicine (NFUM) and the Unani Pharmacopoeia of India (UPI) for the treatment of chronic liver disease were considered and categorized according to their specific therapeutic indications. They were then compared for individual composition, phyto-chemical content, and pharmacological activity. The information thus obtained was useful in identifying plant drugs that are used in a maximum number of formulations and are most valuable in reverting inflammation and fibrotic conditions of advanced-stage liver diseases. The study is intended to provide helpful insights for the development of therapeutic or preventive strategies against HCC.

The Unani formulations used in the treatment of various liver dysfunctions were reviewed from authentic publications of the Central Council for Research in Unani Medicine (CCRUM), Ministry of AYUSH, Government of India. The present study also describes the concept of the liver, its physiology and pathological conditions as given in the Unani system of medicine. This information is derived from classical Unani text *Al Qanoon fit-Tibb* (Hakim Kantoori's Urdu translation),

Moalejaat-e-buqratiya, and Firdaus-ul-Hikmat. Published papers on the concept of the liver in Unani medicine searched from PubMed, and Google Scholar was also reviewed for this description. About four papers were identified that fulfilled the criteria.

The Unani formulations used in the treatment of various liver disorders were reviewed from CCRUM publications namely; National Formulary for Unani Medicine (NFUM) Volume I, II, III, IV, VI¹¹⁻¹⁵ and Unani Pharmacopoeia of India (UPI) Volume II: Part I and Part II¹⁶⁻¹⁷. The eligibility criteria used was to select the formulations that are prescribed for hepatic disorders and having hepatoprotective, hepatotonic, deobstruents, and astringent activity. Formulations used in disorders unrelated to the liver were excluded. Non-traditional, commercially developed formulations that are not part of classical texts are also excluded.

A total of 1091 formulations are described in NFUM and UPI referred volumes out of these 381 were duplicate. So a total of 710 formulations were screened. About 59 formulations fulfilling inclusion and exclusion criteria were selected for the present study. They were grouped based on their mode of action and compared for their composition. The plant drugs which are used in more than seven formulations were identified and reviewed for phytochemical content and pharmacological effect. The published review and research articles on these plants were searched from PubMed and Google Scholar using the terms phytochemical constituents and pharmacological activity. No restriction on years of publication was applied for these searches. A total of 40 relevant articles were identified in this literature search. The reference lists of the retrieved articles were hand-searched to identify additional relevant articles. After a review of the titles, 10 of these records were found to be duplicated and were excluded. The abstracts of the remaining 30 records were reviewed, and a further eight were excluded. The remaining 22 records underwent a full-text review for assessment of eligibility. A total of 21¹⁸⁻³⁸ articles met the eligibility criteria and were included in the systematic review.

The National Formulary of Unani Medicines and Unani Pharmacopoeia of India provides detailed

information on symptoms, diagnosis, and treatment options of various diseases, including all chronic liver diseases. About 12 diseased conditions of the

liver are defined in these texts. They are given in **Table 1** and compared with the counterpart described in the modern system of medicine.

TABLE 1: LIST OF PATHOLOGICAL LIVER CONDITIONS DESCRIBED IN UNANI TEXTS AND ITS COUNTERPART IN MODERN MEDICINE

| S. no. | Unani term | Modern term |
|--------|--|---|
| 1 | <i>Su-ul-Qinaya</i> | Anemia |
| 2 | <i>Yarqan</i> | Jaundice |
| 3 | <i>Istiska</i> | Ascites |
| 4 | <i>Warm-e-Jigar/ kabad</i> | Hepatitis |
| 5 | <i>Dard-e-Jigar / Waj-ul-kabid</i> | Hepatalgia |
| 6 | <i>Tasaddud-e-kabid</i> | Hepatic obstruction |
| 7 | <i>Su-e- Mizaj</i> | Abnormal/ Pathological temperament of the Liver |
| 8 | <i>Zauf-e Jigar/Zof-e-kabid</i> | The dullness of Liver, Hepatosis, or Hypocholeretic/weakness of the liver |
| 9 | <i>Zarba-e-Jigar</i> | Trauma |
| 10 | <i>Dabila-e-Jigar</i> | Hepatic Abscess |
| 11 | <i>Segar-e-jigar</i> | Cirrhosis of Liver |
| 12 | <i>Salabat-e-Tehal&Salabat-e-kabid</i> | induration of spleen/ Liver |

Trauma, inflammation, hepatic obstruction, fibrosis, and regeneration are important features determining the severity of hepatic damage in various chronic liver diseases. Specific treatment regimens are suggested depending on the extent of liver damage. The diagnostic features and the treatment options for each of these conditions are

detailed in classical Unani texts. A total of about 59 compound formulations were described. The composition, method of preparation, mode of action, therapeutic indications, and doses of each formulation were described in detail. The list of these formulations and pathological conditions for which they are used are presented in **Table 2**.

TABLE 2: CLASSICAL UNANI FORMULATIONS PRESCRIBED IN NFUM AND UPI FOR TREATMENT OF VARIOUS CHRONIC LIVER DISEASES

| S. no. | Unani Formulations | Muqa wwi-e-jiger | Waram-e-kabid/ Jigar (hepatitis) | Tasaddud-e-kabid (hepatic obstruction) | Zof-e-kabid (weakness of liver) | Yarqan (jaundice) | Waj-ul-kabid (hepatalgia) | Su-ul-qiniya (anaemia) | Salabat-e-Tehal/ kabid (induration of spleen/ Liver) |
|--------|-----------------------------|------------------|----------------------------------|--|---------------------------------|-------------------|---------------------------|------------------------|--|
| 1 | Araq-e-afsanteen | | √ | √ | | | | | |
| 2 | Araq-e-biranjaisif | | √ | | | | | | |
| 3 | Araq-e-kasni | | √ | | | √ | | | |
| 4 | Dawa-ul-kurkum | | √ | | | | | | |
| 5 | Dawa-ul-luk | | √ | | | | | | √ |
| 6 | Habb-e-barhami | | √ | | √ | | | | |
| 7 | Habb-e-Kabar | | √ | | | | | | |
| 8 | Habb-e-kabidnaushadari | | √ | | | | | | |
| 9 | Habb-e-mazaryun | | √ | | √ | | | | |
| 10 | Majoon-e-Reward | | √ | | | | √ | | |
| 11 | Majoon-e-gul | | √ | | | | | | |
| 12 | Jawarish-e- amla sada | | √ | | | | | | |
| 13 | Qurs-e- sumbul-ut-teeb | | √ | | | | √ | | |
| 14 | Qurs-e-firanjmushk | | √ | | √ | √ | | | |
| 15 | Qurs-e-ghafis | | √ | | | √ | | | √ |
| 16 | Qurs-e-hummaz | | √ | | | | | | |
| 17 | Qurs-e-sumbul | | √ | | | | | | |
| 18 | Sharbat-e-deenar | | √ | | | √ | | | |
| 19 | Tehali | | √ | | | | | | √ |
| 20 | Zimad-e-Iklilulmalik (local | | √ | | | | | | |

| | | | | | | | |
|----|---|---|---|---|--|---|---|
| 21 | application) Majoon-e- Dabidul ward | √ | √ | | | | √ |
| 22 | Qurs-e-zarishk | √ | √ | | | | √ |
| 23 | Jawarish-e-Tamar hindi | √ | | | | | |
| 24 | Majoon-e- jalinooslului | √ | | | | √ | |
| 25 | Qurs-e- ambarbaris | √ | | √ | | √ | |
| 26 | Qurs-e- ambarbaris qawi | √ | | √ | | √ | |
| 27 | Qurs-e-istisqa | √ | | | | | |
| 28 | Qurs-e-kabdi | √ | | | | √ | |
| 29 | Qurs-e-luk | √ | | | | | |
| 30 | Sharbat-e-faulad | √ | | | | | |
| 31 | Sikanjabeen- buzoorimotadil | √ | | √ | | | |
| 32 | Sikanjabeenlemuni | √ | | | | √ | |
| 33 | Sufoof-e-maleh | √ | | | | | √ |
| 34 | Yashbi | √ | | | | √ | |
| 35 | Zimad-e- feesaghorus(local application) | | | | | √ | |
| 36 | Araq-e-mako | | | | | √ | |
| 37 | Fawakeheen | | | | | √ | |
| 38 | Gulqand-e-Gulab | | | | | √ | |
| 39 | Jawarish-e-utraj | | | | | √ | |
| 40 | Jawarish-e- jalinoos | | | | | √ | |
| 41 | Jawarish-e- aamlaambary | | | | | √ | |
| 42 | Jawarish-e- aamlaluluvi | | | | | √ | |
| 43 | Jawarish-e- Darchiniqawi | | | | | √ | |
| 44 | Jawarish-e- fawakeh | | | | | √ | |
| 45 | Jawarish-e- narmushk | | | | | √ | |
| 46 | Jawarish-e- anarain | | | | | √ | |
| 47 | Kushta-e-faulad | | | | | √ | √ |
| 48 | Kushta-e- khabsulhadeed | | | | | √ | |
| 49 | Majoon-e- Buqrat | | | | | √ | |
| 50 | Majoon-e-khabs- ul-hadeed | | | | | √ | √ |
| 51 | Majoon-e- sangdanamurgh | | | | | √ | |
| 52 | Murabba-e-aamla | | | | | √ | |
| 53 | Sabadaritoos | | | | | √ | √ |
| 54 | Sharbaat-e- bazoormotadil | | | √ | | | |
| 55 | Qurs-e-ward | | | √ | | | |
| 56 | Zimad-e-qutoon (local application) | | | | | | √ |
| 57 | Majoon-e- Juntiyana | | | | | | √ |
| 58 | Qurs-e-gul | | | | | √ | |
| 59 | Habb-e-Ghafis | | | | | √ | √ |

The specific pathological condition for which the formulation is recommended has been indicated by a tick.

The above table provides information on 59 formulations used in various stages of liver diseases. The table shows that some formulations

are specific to only particular disease whereas other covers broad range of liver diseases. This specificity of formulations is due to the unique

properties of individual plant drugs. Grossly the formulations could be arranged into six groups based on their mode of action. A large number of formulations are heptatonic (*Muqawwi –e-kabid*) and therefore used in the dullness of the liver (*Zof-e-kabid*). Some formulations such as *Arq-e-kasani*, *Habb-e-ghafis*, *Dawa-ul-luk*, *Qurs-e-ambarbaris* have the deobstructive (*Muffat-e-sudad*) activity and hence find their use in conditions of hepatic obstruction. The formulations such as *Dawa-ul-kurkum*, *Dawa-ul-luk*, *Majoon-e-dabidul ward*, *Sharbat-e-dinar*, and *Qurs-e-kabidi* have Diuretic (*Muddir-e-baul*) activity and are useful in the treatment of ascites. Due to the anti-inflammatory (*Muhalil-e-warm*) property of *Arq-e-afsanteen*, *Ark-e-kasani*, *Habb-e-kabid naushadri*, *Jawarish-e-amlā sada*, *Qurs-e-ghafis*, they are used in hepatitis. The formulations *Dawa-ul-kurkum*, *Dawa-ul-luk*, and *Qurs-e-afsanteen* possess hot temperament hence used in the altered cold temperament of the liver which is responsible for the dullness of liver (*Zof-e-kabid*), ascites (*Istisqa*), and anaemia (*Su-ul-Qinaya*). Lastly, more complex formulations like *Dawa-ul-kurkum*, *Dawa-ul-luk*, *Habb-e-ghafis*, *Majoon-e-dabidul ward*, *Sharbat-e-*

dinar, *Jawarish-e-tamar hindi*, and *Shikanjabeen bazoori motadil* possess multiple properties of diuresis, deobstruction, and astringent and hence are strongly advised for multiple disease conditions.

Comparison of Formulations for Individual Composition:

The formulations enlisted in table 2 were searched for individual components. It was observed that a total of 121 plant drugs, 18 minerals, and 6 animal-derived drugs had been used in the preparation of 59 formulations compiled in **Table 2**. The literature review for research studies undertaken on each of these plants was carried out using various search options. Most of them possessed hepatoprotective potential and were rich in flavonoids, saponins, and tannins. Few plants out of these were extensively investigated and had multiple medicinal properties. Incidentally, these plants were also a constituent of various formulations. Such plants were identified and grouped. **Table 3** presents the plants which are part of multiple formulations for application in various diseased conditions of the liver.

TABLE 3: LIST OF MEDICINAL PLANTS USED IN MULTIPLE FORMULATIONS

| S. no. | Unani name | Botanical name | Common name | Parts used | Temperament | No. of times Used in Formulations |
|--------|---------------------------|--------------------------------|-----------------|--------------------|-------------|-----------------------------------|
| 1 | <i>Sumbul-ut-teeab</i> | <i>Nardostachys jatamanasi</i> | Spikenard | Rhizomes | Hot Dry | 21 |
| 2 | <i>Warq-e-gul-e-surkh</i> | <i>Rosa damascena</i> | Rose | Flowers | Cold Dry | 21 |
| 3 | <i>Rewand chini</i> | <i>Rheum emodi</i> | Indian Rhubarb | Roots and rhizomes | Hot Dry | 18 |
| 4 | <i>Mastagi</i> | <i>Pistacia lentiscus</i> | Mastic | Resin | Hot Dry | 16 |
| 5 | <i>Tukhm-e-Kasni</i> | <i>Cichorium Intybus</i> | Chicory | Seeds | Cold Dry | 16 |
| 6 | <i>Filfil siyah</i> | <i>Piper nigrum</i> | Black pepper | Fruits | Hot Dry | 15 |
| 7 | <i>Zanjabeel</i> | <i>Zingiber officinale</i> | Dry Ginger | Rhizomes | Hot Dry | 13 |
| 8 | <i>Zafran</i> | <i>Crocus sativus</i> | Saffron | Stamens | Hot Dry | 13 |
| 9 | <i>Tukhm-e-karafs</i> | <i>Apium graveolens</i> | Celery | Seeds | Hot Dry | 12 |
| 10 | <i>Darchini</i> | <i>Cinnamomum zeylanicum</i> | Cinnamon | Bark | Hot Dry | 11 |
| 11 | <i>Anisoon</i> | <i>Pimpinella anisum</i> | Aniseeds | Seeds | Hot Dry | 9 |
| 12 | <i>Qust</i> | <i>Saussurea lappa</i> | costus or kuth | Rhizomes | Hot Dry | 9 |
| 13 | <i>Shagufa-e-Izkhar</i> | <i>Cymbopogon jwarancusa</i> | Jwarancusa | Flowers | Hot Dry | 8 |
| 14 | <i>Anarshireen</i> | <i>Punica granatum</i> | Pomegranate | Seeds, Bark | Cold Moist | 8 |
| 15 | <i>Zarishk</i> | <i>Berberis aristata</i> | Indian barberry | Stem, root | Hot Dry | 7 |
| 16 | <i>Tukhm-e-Kasoos</i> | <i>Cuscuta reflexa</i> | Dodder | Whole plant | Hot Dry | 4 |

Table 3 presents a list of plants that are used in multiple Unani formulations for the treatment of chronic liver diseases. The common name, part of the plant used, its temperament and the number of times it is used in formulations are detailed.

Table 3 points out that sixteen medicinal plant drugs out of 121 are used in multiple Unani formulations. Repeated use in elevation of liver dysfunctions underlines the importance of their

medicinal value. Information of chemical composition and biological effect of these plants would be of help in exploring their use in a more complex and severe condition such as HCC. **Table 4** summarised the information of phytochemical content and pharmacological effects of these

sixteen selected plants as obtained through Google and PubMed searches. It will be worthwhile determining their active ingredient and mechanism of action for exploring their use in the management of HCC.

TABLE 4: PHYTOCHEMICAL CONTENT AND BIOLOGICAL EFFECT OF PLANTS LISTED IN TABLE 3

| S. no. | Plant Drugs | Part Used | Phytochemical Composition | Biological Effect and Mechanism |
|--------|---|--------------------|--|--|
| 1 | Sumbul-ut-teeb <i>Nardostachys jatamansi</i> ¹⁸ | Rhizomes | Sesquiterpenoids, terpenic coumarins, lignans, jatamansone or valeranone, alpha-patcho-ulense, angelicin, β -sitosterol, calarene, elemol, jatamansin, jatamansinol, n-hexaco-sanyl, n-hexacosane, oroselol, patchouli alcohol, valeranal, nardostachnol, seychellene, seychelane, nardostachone, volatile oil, resin, sugar, starch, ketone, jatamansic acid, jatamansonesemicarbazone, lupelol, malliene, calarenol, terpenic, coumarin-jatamansin, propionate, cyclohexanal ester, hepatacosanylpentanoate, diethaniod bicyclic-ketone-nardostachone, actidine, Nardal. | Used in Ayurvedic and Unani Systems of medicine for the treatment of liver and CNS disorders. It is used as a stimulant, tonic, antispasmodic, laxative, bronchodilator, vasodilator, and tranquilizer. Investigated properties: Antifungal, hepatoprotective, anticonvulsant, neuroprotective, antiparkinson's, antidepressant, tranquilizing, antioxidant, antidiabetic, antihysterical, hypotensive, antispasmodic, anti-inflammatory, cardiogenic, antimicrobial, vasodilator, antiepileptic. |
| 2 | Warq-e-gul-e-surkh <i>Rosa damascena</i> ¹⁹ | Flowers | Tannin, flavonoids, glycosides, carboxylic acid, ascorbic acid, a long polyunsaturated fatty acid having formula $C_{37}H_{64}O_2$ is an active constituent, cyanidin-3-O- β -glucoside, quercetin, gentiobioside, maurones, rugaurone, maritimein, tetrahydroxyaurone, siamaurone, damaurone. | Used in Unani system of medicines for pain management, digestive problems, menstrual bleeding, and strengthening of the heart. Anti-inflammatory agent in managing and treating various inflammatory conditions. Properties: Significant analgesic, anti-inflammatory, cardiogenic, anti-HIV, antibacterial, antioxidant, antitussive, hypnotic, antidiabetic, relaxant, analgesic, laxative, wound healing, skin tonic, gastrointestinal diseases, menstrual bleeding, pregnancy-related disorders, mental disorder, depression, anxiety. Beneficial for liver dysfunction and have liver tonic properties. Induced neurite outgrowth activity and inhibited A β induced atrophy and cell death. -Isolation of long -Protects A β (25-35) induced atrophy and displayed strong neurite outgrowth activity. |
| 3 | Rewand chini <i>Rheum emodi</i> ²⁰ | Roots and rhizomes | Anthraquinones, emodin, chrysophanol, aloe-emodin, rhein, physcion, charysophanol, piceatannol, resveratrol, oxanthrone esters. | Anticancer properties against breast cancer, liver cancer, lung squamous cell carcinoma, gastric cancer, colon cancer, prostate cancer, melanoma, leukemia and lymphoma cell lines. It shows these activities by arresting cell cycle, regulation of Bid, Bcl-2, Bcl-xL, Fas, P21, Bcl-2 proteins, activation of caspase, loss of mitochondrial potential, and release of cytochrome c. It also has antioxidant, anti-inflammatory, antimicrobial, antifungal, antiplatelet, antidiabetic, antiulcer, hepatoprotective, immune booster, nephroprotective activities. |
| 4 | Mastagi | Resin | Beta pinene, Alpha pinene, catechin, | Anticancer, hepatoprotective, |

| | | | | |
|----|--|------------------|--|--|
| 5 | <i>Pistacia lentiscus</i> ²¹ Tukhm-e-Kasni <i>Cichorium intybus</i> ²² | Fruits, Seeds | verbenone, thymol, limonene, terpene, carvacrol, gallic acid, myreene, linalool, Alpha tocopherol. Sesquiterpene lactones (Lectucin, Lactucopicrin, 8-desoxy lactucin, guianolid glycosides, including chicoroides B and C sonchuside C), caffeic acid derivatives (chicoric acid, chlorogenic acid, isochlorogenic acid, dicaffeoyl tartaric acid), inulin, sugars, proteins, hydroxycoumarins, flavonoids, alkaloids, steroids, terpenoids, oils, volatile compounds, Coumarin, and vitamins. | antiatherogenic, antimicrobial, antioxidant, anti-tumor antiarthritic, antigout, hypotensive, antifungals. Hepatoprotective, gastroprotective hypolipidaemic, anticancer, anti-inflammatory, wound healing. Significant histological damage (steatosis, inflammation, fibrosis) to the cells and tissues are reverted via downregulation of SRVEP_1c and PPAR α genes that follow steatosis induction. Inhibition of PGE2, TNF α dependent induction of COX -2 induction and activation of Nf- kappa B in human colon carcinoma cell line. |
| 6 | Filfil siyah <i>Piper nigrum</i> ²³ | Fruits | Alkaloids, lignans, terpenes, piperine, propanedioic acid, dimethyl ester, bicycloheptane, 3-Carene, Cyclohexene ethylpyrrolidine, L- α -Terpineol, lavandulyl acetate, Pyrrolizine-ethyl(ester), Eugenol, alfa. Copaene, epiglobulol, Caryophyllene, α -langene, β -copaeneisocalamendiol. | CNS depressant, antipyretic, analgesic, anti-inflammatory, antioxidant, hepatoprotective, anti-tumor, anti-helicobacter pylori, anti-candida, anti-aging, anti-hyperlipidemia, Anti-termitic, anti-osteoporosis, antiulcer, antiatherosclerotic, anti-HIV. |
| 7 | Zanjabeel <i>Zingiber officinale</i> ²⁴ | Rhizomes | Gingerols, shogaol, paradol, gingerdione, zerumbone. | Reduced the elevated expression of tumor necrosis factor –Alfa (TNF- α) and NF-kB by extract ginger in liver cancer of rat. Hepatoprotective, cytotoxic, nephroprotective, larvicidal, anti-bacterial, anti-diarrhea, antidiabetic, antioxidant, anthelmintic, anti-fungal, anti-inflammatory, analgesic |
| 8 | Zafran <i>Crocus sativus</i> ²⁵ | Stamens | Crocin, crocetin, afraanal picrocrocin. | Crocin enhances apoptosis by raising the Bax/Bcl-2 ratio in gastric cancer. Inhibit nuclear factor-kappa b activation, increase cleavage of caspase-3 as well as DNA damage. Antihypertensive, anticonvulsant, antitussive, antigenotoxic, anxiolytic, aphrodisiac, antioxidant, antidepressant antinociceptive, relaxant, anticancer for skin cancer, cervical cancer, leukemia, breast cancer, colorectal cancer, liver cancer, pancreatic cancer. |
| 9 | Tukhm-e-karafs <i>Apiumgraveolens</i> ²⁶ | Seeds | Carbohydrates, flavonoid, alkaloids, steroids, glycosides, phenols, furocoumarins, celerin, furocoumarins, limonene (60%), β -pinene, camphene, cymene, limonene, α -pinene, β -phellendrene, p-cymene, γ -terpinene, phthalide sabinene, α -pinene, myristic, linoleic, petroselinic, palmitoleic, palmitic, oleic, myristoleic, stearic acid, santalol, β -eudesmol, α -eudesmol, sedanenolide. | An antioxidant inhibitory effect on hepatocarcinogenesis, anti-inflammatory, cytotoxic, antimicrobial, hypolipidaemic. |
| 10 | Darchini <i>Cinnamomum zeylanicum</i> ²⁷ | Bark | Proanthocyanidin compound, procyanidin B2. | Anti-allergenic, anti-inflammatory, antipyretic, antibacterial, antifungal, anesthetic, antioxidant ²⁷ . CE and specific characterized CE components, type A procyanidin trimer and tetrameric procyanidins, effectively |

| | | | | |
|----|--|-------------|---|--|
| | | | | inhibited VEGFR2 kinase activity as well as VEGF signaling in endothelial Cells ²⁸ |
| 11 | Anisoon <i>Pimpinella anisum</i> ²⁹ | Seeds | Anethol, Alkaloids, flavonoids, saponins, tannins, terpenoids, phenolic compounds, cardiac glycosides. | Diuretic, laxative, expectorant, anti-spasmodic, antioxidative, anti-diabetic. ²⁹ Anethol can suppress NF- κ B activation through the inhibition of I κ B α degradation ³⁰ |
| 12 | Qust <i>Saussurea lappa</i> ³¹ | Rhizomes | Resins, alkaloids, steroids, flavonoids, costunolide, antamarine, Isaussureamines, chrysophanol. | Antioxidant, anti-inflammatory, anticancer, antitumor, hepatoprotective, hypnotic, analgesic, antiaging, immunomodulatory ³¹ . TNF α -induced cell migration and invasion were inhibited by either costunolide. suppressed TNF α -induced NF- κ B translocation to the nucleus and transcriptional activity. Besides, costunolide specifically inhibited IKK phosphorylation and I κ B α degradation ³² |
| 13 | Shagufa-e-Izkhar <i>Cymbopogon jwarancusa</i> ³³ | Flowers | Citronellal, piperitone, geraniol, pentatriacontane, 6- pentatriacontanone, elemal. | Antioxidant, anti-allergic, antimicrobial, antiparasitic, analgesic, and antipyretic. |
| 14 | Anar <i>Punica granatum</i> ³⁴ | Seeds, Bark | Tannins, saponins, Quinone, terpenoids, steroids, phenols, flavonoids, alkaloids, glycosides, anthocyanin, betacyanin. | Antiviral, antioxidant, estrogen depletion, anticancer, anti-inflammatory. Suppress NF- κ B activation ³⁰ |
| 15 | Zarishk <i>Berberis aristata</i> ³⁵ | Stem, root | Berberine, oxyberberine, berbamine, aromoline, palmatine, oxycanthine, taxilamine, alkaloids, reducing sugar, Coumarin, saponins, flavonoids, steroids, glycosides, tannin, polyphenol, terpenoids. | Hypoglycaemic, antibacterial, anti-fungal, hepatoprotective, anti-cancer, anti-diarrhoeal, anti-inflammatory, anti-microbial, anti-pyretic, anti-oxidant, antimalarial, immunomodulatory ³⁵ . TNF- α induced cell invasion is prevented by berberine treatment in a human breast cancer cell. Berberine prevent MMP- 9 induced degradation of ECM including type IV collagen, leading to inhibition of AP-1 DNA binding activity ³⁶ |
| 16 | Tukhm-e-Kasoos <i>Cuscuta reflexa</i> ³⁷ | Whole plant | Alkaloids, flavonoids, terpenoids, fixed oil, phytosterols, saponins, fats, carbohydrates, protein, glycoside. Cuscutalin (1%) and cuscutin (0.02%). quercetin, amarbelin, amino acids, scoparone, melanettin, hyperoside, aromadendrin, taxifolin, astragalgin | Anti-inflammatory, anticancer, antimicrobial, antifungal, hypotensive, hypoglycaemic ³⁷ . It blocked NF- κ B binding to its motifs and induced apoptosis in Hep3B cells. It upregulated pro-apoptotic factors BAX and p53 and down-regulated anti-apoptotic factor Bcl-2 ³⁸ |

Table 4 Phytochemical content and biological effects of plants used in various Unani formulations for the treatment of chronic liver diseases.

In addition to the plants listed in **Table 3**, few others (not mentioned in **Table 3**) are also a part of multiple formulations. They are namely; *Citrus aurantifolia*, *Pimpinella anisum*, *Trachyspermum ammi*, *Foeniculum vulgare*, *Myristica fragrans*, *Piper nigrum*, *Rosa damascene*, *Amomum subulatum*, *Elettaria cardamomum*, *Portulaca oleracea*, *Mentha arvensis*, *Aloe barbadensis*, *Citrus medica*, and *Zingiber officinale*. Most of these are herbs or spices used in the diet. They are rich in essential oils and are known for preventing oxidative damage and suppress inflammation.

They are also known to possess a spectrum of biological activity. They are used for antioxidant and anti-inflammatory effects in addition to flavoring agents in complex formulations.

The other plants referred to in **Table 4** such as *Saussurea lappa*, *Rheum emodi*, *Cinnamomum zeylanicum*, *Berberis aristata*, *Nardostachy jatamanasi*, *Crocus sativum*, *Piper nigrum*, *Cuscuta reflexa*, *Pistacia lentiscus*, *Cichorium intybus*, *Apium graveolens*, *Pimpinella anisum*, are rich in polyphenols, lignin, flavonoids and possess

a broad spectrum of biological activities. They have demonstrated inhibition of cell proliferation and induction of caspase-3 dependent apoptosis of cancer cell lines *via* vital signaling pathways. Few of them induced apoptosis by inhibiting topoisomerase I or II, which are nuclear enzymes that control DNA supercoiling during DNA replication and transcription. The study suggests that these 16 plants are likely to have high anti-tumour potential to combat the cancer cells of liver. Extensive studies for these plants should provide insight into pharmaceutical efficacy for the prevention and therapy of HCC.

CONCLUSION: The present study attempted to review the formulations described in the National Formulary of Unani Medicine and Unani Pharmacopoeia of India for the treatment of liver diseases. A total of fifty-nine formulations were described. They were grouped into six groups based on their biological action and medicinal value. The comparison of these formulations for composition identified that they were prepared using 121 plant drugs, 18 minerals, and 6 animal-derived products. About sixteen plant drugs out of these had a profound biological effect and were used in multiple formulations for treatments of mild to severe conditions of the liver. The review points out that these sixteen plants having potential bioactive compounds, pharmacological effects and clinical application should be explored for the development of newer effective drugs in the treatment of hepatocellular carcinoma.

ACKNOWLEDGEMENT: The authors are grateful to CCRUM, Ministry of AYUSH, Government of India for sanction of research grant for this study. The authors are also grateful to Dr. S. A. Shaikh, Principal, Rajiv Gandhi Institute of IT & Biotechnology for facilitating this study. We are thankful to Ms. Rukhsar Khan and Ms. Kunjal Rathod for their assistance in referencing this paper.

CONFLICTS OF INTEREST: No competing financial interests exist.

REFERENCES:

- Ozougwu and Jevas C: Physiology of the liver. International Journal of Research in Pharmacy and Biosciences 2017; 4(8): 13-24.
- Hong M, Li S, Tan HY, Wang N, Tsao SW and Feng Y: Current status of herbal medicine in chronic liver disease therapy: The biological effects, molecular targets and future prospect. International Journal of Molecular Science 2015; 16(12): 28705-45.
- Setiawan VW, Stram DO, Porcel J, Lu SC, Le Marchand L and Nouredin M: Prevalence of chronic liver disease and cirrhosis by underlying cause in understudied ethnic groups: The multi-ethnic cohort. Hepatology 2016; 64(6): 1969-77.
- Brian I and Carr: Understanding liver cancer: A tale of two diseases. Springer healthcare communications London, UK, First edition, 2014: 1-16.
- Sina I: Al Qanoon fit tib. (Urdu translation by Ghulam Hussain Kantoori). Idara kitabushifa publication, New Delhi, Vol 3 2010.
- Tabri AHAM: Al molejaatbukratiya. Vol 3. Central council for research in Unani medicine New Delhi, Vol 3, 1997: 197-217.
- Tabri AHR: Firdausulhikmat (Urdu), Sheikh Mohammad Bashir & sons, Lahore, 1 & 21997: 206-210
- Ansari S, Siddiqui MA and Fasihuzzaman: Therapeutic principles of liver diseases in Unani medicine. Journal of Research and Education in Indian Medicine 2015; XXI: 101-05.
- Siddiqui A, Anjum R, Jamal A, Aslam M and Choudhary SS: Fatty liver diseases in Unani system of medicine. International Journal Pharmacy Med Biology allied Science 2017; 1-9
- Siddiqui MA and Ansari S: Unani treatment improved fibrosis in decompensated cirrhosis of liver: A case series. Journal of Ayurveda and Integrative Medicine 2015; 4(2): 61-66.
- National Formulary of Unani Medicine: Central Council for Research in Unani Medicine, Ministry of health and F. W. (Dept. of AYUSH) publication, Delhi, First reprint Part 1, 2006.
- National Formulary of Unani Medicine: The controller of publications: civil lines, Delhi, First edition, Part III, 2001.
- National Formulary of Unani Medicine: The controller of publications civil lines, Delhi, First edition, Part IV, 2006.
- National Formulary of Unani Medicine: Central Council for Research in Unani Medicine Delhi, First edition. Part VI, 2011.
- National Formulary of Unani Medicine: Dept. of AYUSH, Ministry of Health & Family Welfare, Govt. of India, First edition, Part II(I), 2007.
- Unani Pharmacopoeia of India: Central Council for Research in Unani Medicine, Part II(I), 2009.
- Unani Pharmacopoeia of India: Central Council for Research In Unani Medicine, Part II(II), 2010.
- Purnima, Bhatt M and Kothiyal P: A review article on phytochemistry and pharmacological profiles of *Nardostachy jatamanasi* DC-medicinal herb. Journal of Pharmacognosy and Phytochemistry 2015; 3(5): 102-06.
- Ali M, Sultana S and Jameel M: Phytochemical investigation of flowers of *Rosa damascene* Mill. International Journal of Herbal Medicine 2016; 4(6): 179-83.
- Rehman H, Begum W, Anjum F and Tabasum H: *Rheum emodi* (Rhubarb): A fascinating herb. Journal of Pharmacognosy and Phytochemistry 2014; 3(2): 89-94.
- Nahida, Ansari SH and Siddiqui AN: *Pistacia lentiscus*: A review on phytochemistry and pharmacological properties. International Journal of Pharmacy and Pharmaceutical Science 2012; 4: 16-20.

22. Shaikh T, Mujum A, Khan W and Rub RA: An overview on phytochemical and pharmacological profile of *Cichorium intybus* Linn. Pharmacology Online 2010; 298-307.
23. Mohammed GJ, Omran AM and Hussein HM: Antibacterial and phytochemical analysis of *Piper nigrum* using gas chromatography – Mass spectrum and fourier-transform infrared spectroscopy. International Journal of Pharmacy and Pharmaceutical Research 2016; 8(6): 977-96.
24. Kumar G, Karthik L and Rao KVB: A review on pharmacological and phytochemical properties of *Zingiber officinale* Roscoe (Zingiberaceae). Journal of Pharmacy Research 2011; 4(9): 2963-66.
25. Bhandari PR: *Crocus sativus* L. (Saffron) for cancer chemoprevention: A mini review. Journal of Traditional and Complementary Medicine 2015; 5: 81-87.
26. Rakad M and AL-Jumaily K: Evaluation of anticancer activities of crude extracts of *Apium graveolens* L. seeds in two cell lines, RD and L20B in vitro. Iraqi Journal of Cancer and Medical Genetics 2010; 3(2): 18-23.
27. Varalakshmi B, Anand AV, Karpagam T, Bai JS and Manikandan R: *In-vitro* antimicrobial and anticancer activity of *Cinnamomum zeylanicum* Linn bark extract. International J of Pharm and Pharma Scie 2014; 6: 12-18.
28. Lu J, Zhang K, Nam S, Anderson RA, Jove R and Wen W: Novel angiogenesis inhibitory activity in cinnamon extract blocks VEGFR2 kinase and downstream signalling. Carcinogenesis 2010; 31(3): 481-88.
29. Islam ZM, Khan K, Mahdi SR and Chowdhury IM: Antibacterial and phytochemical screening of *Pimpinella anisum* through optimized extraction procedure. Asian Journal of Science and Technology 2016; 7(11): 3912-18.
30. Bharat B, Aggarwal and Shishir S: Suppression of the nuclear factor-kB activation pathway by spice-derived phytochemicals. Annals of the NewYork Academy of Science 2004: 434-41.
31. Choudhary GP: Phytochemical and pharmacological study of *Saussurea lappa* Clarke: A review. European Journal of Pharmaceutical and Medical Research 2015; 2(7): 120-25.
32. Choi YK, Cho SG, Woo SM, Yun YJ, Jo J and Kim W: *Saussurea lappa* clarke-derived costunolide prevents TNF α -induced breast cancer cell migration and invasion by inhibiting NF-kB activity. Evidence Based Complementary and Alternative Medicine 2013; 1-10.
33. Prasad C, Singh D, Shukla O and Singh UB: *Cymbopogon jwarancusa* - An important medicinal plant: A review. Pharma Innovation Journal 2014; 3(6): 13-19.
34. Jayaprakash A and Sangeetha R: Phytochemical screening of *Punica granatum* Linn. peel extracts. Journal of Artificial Intelligence and Research 2015; 4(5): 160-62.
35. Lamichhane B, Adhikari S, Shrestha P and Shrestha BG: Study of phytochemical, antioxidant, antimicrobial and anticancer activity of *Berberis aristata*. J Tropical Life Science Research 2014; 4(1): 01-07.
36. Kim S, Choi JH, Kim JB, Nam SJ, Yang JH and Kim JH: Berberine suppresses TNF- α -induced MMP-9 and cell invasion through inhibition of AP-1 activity in MDA-MB-231 human breast cancer cells. Molecules 2008; 13: 2975-85.
37. Chatterjee D, Sahu RK, Jha AK and Dwivedi J: Evaluation of antitumor activity of *Cuscuta reflexa* Roxb (Cuscutaceae) against ehrlich ascites carcinoma in swiss albino mice. Tropical Journal of Pharmaceutical Research 2011; 10(4): 447-54.
38. Ashwani K, Sapna R, Somiya S and Niketa: Recent review on plant molecular biology, phytophysiology, phytochemistry and ethonopharmacology of *Cuscuta reflexa* Roxb. a wonderful parasitic plant. International Research Journal of Pharmacy 2012; 3(7): 30-38.

How to cite this article:

Shaikh ZA, Kamyab SS, Deshpande MM, Mulla GJ, Bhatt NS and Moghe AS: A systematic review of Unani formulations for potential in treatment of hepatocellular carcinoma. Int J Pharm Sci & Res 2021; 12(10): 5253-63. doi: 10.13040/IJPSR.0975-8232.12(10).5253-63.

All © 2021 are reserved by the International Journal of Pharmaceutical Sciences and Research. This Journal licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 3.0 Unported License.

This article can be downloaded to **Android OS** based mobile. Scan QR Code using Code/Bar Scanner from your mobile. (Scanners are available on Google Playstore)